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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
STOLE, E	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/828,323	Applicant(s) O'Donnell
	Examiner Einar Stole	Group Art Unit 1652

☒ Responsive to communication(s) filed on *Jan 5, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *5-75* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *5-75* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Claim 1 has been canceled by the Amendment of August 5, 1998, entered on January 5, 1998 as Paper No. 12. Claims 5-75 are presented for examination.

Specification

2. The amendment filed on August 5, 1997 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: 1) the deletions and replacements made on page 17 at lines 26, 27, and 28, and 2) the replacement sequence listing (both paper copy and CRF) which includes modification of the sequence of SEQ ID NO: 54.

3. Applicant is required to cancel the new matter in the reply to this Office action.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Although the nucleotide and/or amino acid sequence disclosure contained in this application **does comply** with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825, the submitted paper copy and computer readable form (CRF) of the sequence listing contain new matter. Thus, a substitute

paper copy and CRF must be submitted, as required by 37 C.F.R. 1.825(d), which removes the amendments to the original sequence submission identified above as new matter. Applicants should also submit a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

The applicant is encouraged to call (703) 308-4216 regarding any inquiry concerning rules interpretation, (703) 308-4212 for CRF submission help, and (703) 308-6856 for PatentIn software help.

Claim Objections

5. Claims 8, 10, 17, 22, 26, 28, 33, 44, 48, 55, and 62 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

6. Claim 18 is objected to because of the following informalities: "too", appearing in line 1 of claim 18 is misspelled and should be replaced with --to--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 9, 11, 18-20, 23, 27, 29, 34, 38, 40, 45, 49, 51, 56, and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 9, 11, 27, 29, 38, 40, 49, 51, and 63 are drawn to isolated DNA molecules, including expression systems and transformed host cells thereof, which are defined by a specific SEQ ID NO (specifically SEQ ID NO: 6, 13, 29, 39, and 50, and the nucleic acids encoding the proteins described by SEQ ID NO: 9, 10, 32, 38, and 53), but contain **mutations, deletions or additions to these specific sequences**. Thus, the instant claims read on DNA molecules of any sequence which encode proteins of **any** amino acid sequence which have the functional properties of the claimed *Escherichia coli* polymerase III holoenzyme subunits.

Claims 18-20, 23, 34, 45, and 56 are drawn to isolated *Escherichia coli* polymerase III holoenzyme subunits described by specific SEQ ID NO (specifically SEQ ID NO: 9, 10, 32, 38, and 53), but also contain **mutations, deletions or additions to these specific sequences**. Thus, the instant claims read on proteins of **any** sequence which have the functional properties of the specifically claimed *Escherichia coli* polymerase III holoenzyme subunits.

The instant disclosure is enabling for claims limited to: 1) the isolated DNA molecules encoding the δ, δ', θ, ψ, and χ protein subunits of polymerase III holoenzyme; 2) the isolated nucleic acids described by SEQ ID NO: 6, 13, 29, 39, and 50; 3) the isolated nucleic acids encoding the proteins described by SEQ ID NO: 9, 10, 32, 38 and 53; 4) the isolated protein subunits δ, δ', θ, ψ,

and χ of the *Escherichia coli* polymerase III holoenzyme, and 5) the isolated proteins described by SEQ ID NO: 9, 10, 32, 38, and 53. The scope of the instant claims is not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require **undue** experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to: 1) the isolated nucleic acids described by SEQ ID NO: 6, 13, 29, 39, and 50 which contain **mutations, deletions or additions to these specific sequences**; 2) the isolated nucleic acids encoding the proteins described by SEQ ID NO: 9, 10, 32, 38 and 53 which contain **mutations, deletions or additions to these specific sequences**, and 3) the isolated proteins described by SEQ ID NO: 9, 10, 32, 38, and 53 which contain **mutations, deletions or additions to these specific sequences**.

The factors to be considered in determining whether **undue** experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary,

(2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406). Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

In the instant case, claims 9, 11, 18-20, 23, 27, 29, 34, 38, 40, 45, 49, 51, 56, and 63 are broader than the enablement provided by the disclosure with regard to: 1) the extremely large number of claimed polypeptides with the functional properties of the claimed polymerase III subunits δ, δ', θ, ψ, and χ, and 2) the extremely large number of DNA molecules, and expression systems and transformed host cells thereof, which encode polypeptides with the functional properties of the claimed polymerase III subunits δ, δ', θ, ψ, and χ. For example, the isolated protein described by SEQ ID NO: 9 contains 343 amino acids. Thus, the instant claims encompass all polypeptides which encode a functional *Escherichia coli* polymerase III holoenzyme subunit δ. Specifically, the claims encompass any polypeptide described by SEQ ID NO: 9 in which up to 343 amino acids are substituted by any of 20 natural protein amino acids. This corresponds to at least 2×10^{344} possible embodiments, many of which will be inoperative. Although the synthesis and screening of the 2×10^{344} claimed polypeptides constitutes a considerable amount of experimentation, the instant specification discloses no specific amino acid residues which may be modified to produce a functional δ subunit. The prior art does not teach designer, engineered δ subunits. The difficulty of predicting the functional effects of random single amino acid substitutions is well known in the art. In discussing the relationship between particular amino acid substitutions and biological activity, Rudinger (U) states that "the significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." (see page 7, conclusion). Although the state of the art has advanced significantly since the publication of Rudinger (U), these advances are primarily technical, enabling

an artisan of ordinary skill in the art to produce nearly any mutant or variant protein in quantity. Rudinger (U) states merely that the effects of any one mutation, much less multiple mutations, on biological activity is unpredictable without additional experimentation relating the structure of the protein to its biological function. The relationship between the sequence of a peptide and its tertiary structure (i.e., its activity) are not well understood and are not easily predictable (see Ngo et al. (V)) and the state of the art is still such that a skilled artisan cannot predict biological function, *a priori*, from the protein primary structure. Thornton et al. (W) discuss the current state of the art of protein engineering. (see pages 367-369). Specifically, with regard to the unpredictability of relating a protein sequence to either its tertiary structure or biological or enzymatic activity, *a priori*, Thornton et al. (W) state:

> The Oxford dictionary definition of an engineer is one with expertise in design, construction and maintenance. The evidence to date shows that although we are still not very good at design--but learning and improving all the time--the experimental construction and maintenance of any protein sequence is now possible. The challenge is to design proteins with required structures and functions to use as tools in the laboratory and to benefit society in medicine, industry and agriculture. (see Thornton et al. (W), page 369, column 2, paragraph 1, lines 1-9).

Thus, the state of the art at the time the invention was made was such that one of ordinary skill in the art could produce any addition, deletion or substitution variant of the δ subunit of the polymerase III holoenzyme, which, if combined with sufficient guidance to identify functionally relevant amino acid residues, would not constitute undue experimentation. In the absence of guidance relevant to structural or sequence homology information, either in the instant specification or prior art, it is nearly

impossible to predict the functional effects of single amino acid substitutions, additions or deletions, much less substitutions, additions or deletions involving multiple amino acids.

In addition to quantity of experimentation, guidance, relative skill of those in the art and the predictability or unpredictability of the art, as discussed in *Wands*, the nature of the invention is also an important factor. For example, the determination that undue experimentation was not required to make the claimed invention in *Wands* was based primarily on the nature of the invention. (*Wands*, 8 USPQ2d 1406). Although the nature of the monoclonal antibody technology discussed in *Wands* requires considerable screening of hybridomas, protein engineering is based on the relationship between the structure and function of a protein molecule and only requires limited screening of rationally engineered proteins which are based on functional and/or structural information, not large-scale screening of randomly generated proteins.

> Lately site-directed methods have opened up the possibility of engineering virtually any protein. There is, however, a danger that a 'shotgun' approach will prove wasteful of effort. Useful protein engineering requires careful consideration of informative substitutions... ." (see Wallace (X), page 514, column 1, paragraph 3, lines 5-11).

Thus, in view of the lack of working examples, lack of guidance in the specification and the prior art, the unpredictability and nature of the art of protein engineering and the great breadth of the claims, the expectation that one of ordinary skill in the art would successfully obtain the claimed invention without **undue** experimentation is extremely low.

In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein

with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify and isolate other polypeptides with δ subunit functionality, it certainly would require undue experimentation to make their corresponding DNA, vectors and transformed host cells. Therefore, the entire scope of the instant claims is not enabled.

9. Claims 69 and 70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 69 and 70 are drawn to a protein subunit that shares at least 27% or 49% sequence identity, respectively, with another subunit of a polymerase III holoenzyme.

The instant specification does not enable a skilled artisan to make the invention, because the specification does not disclose the methods, algorithms and parameters necessary to determine the claimed degree of sequence identity.

10. Claims 5-7, 9, 12, 13, 25, 30, 31, 36, 41, 42, 47, 52, 53, 59, 64, and 65 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 5-7, 9, 12, 13, 25, 30, 31,

36, 41, 42, 47, 52, 53, 59, 64, and 65 are drawn to DNA molecules, including expression systems and transformed host cells, which encode the δ, δ', θ, ψ, and χ subunits of any DNA polymerase III.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.,* 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin). Similarly, the instant claims define the components of the claimed composition only by their functional properties. The Court held this sort of functional definition insufficient to adequately describe the claimed product.

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. In claims to genetic material, however, a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art, therefore, cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. *University of California v. Eli Lilly*, 43 USPQ2d at 1406.

In the instant case, claims 5-7, 9, 12, 13, 25, 30, 31, 36, 41, 42, 47, 52, 53, 59, 64, and 65 do not specifically define, in structural terms, any of the DNA polymerase III subunits, δ, δ', θ, ψ, and χ, from any other source than *Escherichia coli*. Thus, while the instant claims are directed to a genus of DNA molecules encoding DNA polymerase III subunits, the specification fails to provide any representative species of such subunits. Moreover, the specification fails to describe any representative species by any identifying characteristics or properties other than the functionality of the subunit encoded by the claimed DNA molecules. Given this lack of representative DNA species, Applicants have failed to sufficiently described the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

11. Claims 14-16, 21, 24, 32, 35, 43, 46, 54, 57, and 66-75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 14-16, 21, 24, 32, 35, 43, 46, 54, 57, and 66-75 are drawn to the δ, δ', θ, ψ, and χ subunits of any DNA polymerase III.

The instant claims define the components of the claimed composition only by their functional properties. Claims 14-16, 21, 24, 32, 35, 43, 46, 54, 57, and 66-75 do not specifically define, in structural terms, any of the DNA polymerase III subunits, δ, δ', θ, ψ, and χ, from any other source than *Escherichia coli*. Thus, while the instant claims are directed to a genus of DNA polymerase III subunits, the specification fails to provide any representative species of such subunits. Moreover, the

specification fails to describe any representative species by any identifying characteristics or properties other than the functionality of the subunit encoded by the claimed DNA molecules. Given this lack of representative protein species, Applicants have failed to sufficiently described the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 66-75 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 69 and 70 are drawn to a protein subunit that shares at least 27% or 49% sequence identity, respectively, with another subunit of a polymerase III holoenzyme.

The instant specification does not teach a specific algorithm or parameters required to calculate the claimed sequence identity. For example, the necessary parameters required to calculate the claimed sequence identity, using a disclosed, given algorithm, include gap penalties and mismatch penalties. Since a variety of methods or algorithms and parameters for calculating sequence identity, similarity or homology are known in the art, an explicit teaching of how these calculations are made is required to interpret the claim. A table or figure exemplifying a sequence alignment and the numerical "% sequence identity", without more elaboration, does not satisfy the need for explicit instructions on how to interpret the claim, because it is not possible to work backward from the example to derive the algorithm and parameters used.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 32-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshikawa et al. Claims 32-35 are drawn to the isolated, segregated ψ subunit of the DNA polymerase III from *Escherichia coli.*

Yoshikawa et al. teach the *E. coli rimI* gene. The claimed sequences, the 137 amino acids of SEQ ID NO: 38, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The claimed ψ subunit of the DNA polymerase III from *Escherichia coli.*, corresponding to SEQ ID NO: 38, is identical to the translated nucleotide sequence taught by Yoshikawa et al. and corresponds to SEQ ID NO: 39. Applicant's arguments, filed on January 5, 1998 as Paper No. 12, have been fully considered but they are not persuasive. Applicants argue that Yoshikawa et al. do not teach the unsegregated ψ subunit of the DNA polymerase III subunit and that the nucleotide sequence disclosed by Yoshikawa et al. represents only a fragment of the gene encoding the ψ subunit. Sequence analysis of the nucleotide sequences disclosed by Yoshikawa et al. show that a sequence taught by Yoshikawa et al. is identical to the nucleotide sequence described by SEQ ID NO: 39 which corresponds to the amino acid sequence described by SEQ ID NO: 38.

16. Claims 36, 37, 39, 41, and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Yoshikawa et al. Claims 36, 37, 39, 41, and 42 are drawn to the DNA molecules encoding the isolated, segregated ψ subunit of the DNA polymerase III from *Escherichia coli.*

Yoshikawa et al. teach the *E. coli rimI* gene. The claimed sequence, the 411 nucleotides of SEQ ID NO: 39, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The claimed DNA molecule, corresponding to SEQ ID NO: 39 and the nucleic acids encoding the proteins described by SEQ ID NO: 38, are identical to the translated nucleotide sequence taught by Yoshikawa et al. Applicant's arguments, filed on January 5, 1998 as Paper No. 12, have been fully considered but they are not persuasive. Applicants argue that Yoshikawa et al. do not teach the unsegregated ψ subunit of the DNA polymerase III subunit and that the nucleotide sequence disclosed by Yoshikawa et al. represents only a fragment of the gene encoding the ψ subunit. Sequence analysis of the nucleotide sequences disclosed by Yoshikawa et al. show that a sequence taught by Yoshikawa et al. is identical to the nucleotide sequence described by SEQ ID NO: 39 which corresponds to the amino acid sequence described by SEQ ID NO: 38.

17. Claims 43, 45, and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Stirling et al. Claims 43, 45, and 46 are drawn to the isolated, segregated χ subunit of the DNA polymerase III from *Escherichia coli.*

Stirling et al. teach the *Escherichia coli xerB* gene. The claimed sequence, the 147 amino acids of SEQ ID NO: 53, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The claimed χ subunit, corresponding to SEQ ID NO: 53 are identical to the translated nucleotide sequence taught by Stirling et al. Applicant's arguments, filed on January 5, 1998 as Paper No. 12, have been fully considered but they are not persuasive. Applicants argue that Yoshikawa et al. do not teach the DNA polymerase III holoenzyme or the unsegregated χ subunit. Sequence analysis of the nucleotide sequences disclosed by Stirling et al. show that a sequence taught by Stirling et al. is 96.4% identical to the nucleotide sequence described by SEQ ID NO: 50 which corresponds to 100% sequence identity with the amino acid sequence described by SEQ ID NO: 53.

18. Claims 47, 49, 50, 51, 52 and 53 are rejected under 35 U.S.C. 102(b) as being anticipated by Stirling et al. Claims 47, 49, 50, 51, 52 and 53 are drawn to the DNA molecules encoding the isolated, segregated χ subunit of the DNA polymerase III from *Escherichia coli.*

Stirling et al. teach the *Escherichia coli xerB* gene. The claimed sequence, the 441 nucleotides of SEQ ID NO: 50, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The claimed DNA molecule, corresponding to SEQ ID NO: 50 and the nucleic acids encoding the proteins described by SEQ ID NO: 53, are 96.4% identical to the nucleotide sequence taught by Stirling et al. Applicant's arguments, filed on January 5, 1998 as Paper No. 12, have been fully considered but they are not persuasive. Applicants argue that Yoshikawa et al. do

not teach the DNA molecules encoding the unsegregated χ subunit of the DNA polymerase III and that the nucleotide sequence disclosed by Stirling et al. represents only a fragment of the gene encoding the χ subunit. Sequence analysis of the nucleotide sequences disclosed by Stirling et al. show that a sequence taught by Yoshikawa et al. is 96.4% identical to the nucleotide sequence described by SEQ ID NO: 50, and corresponds to 100% sequence identity with the amino acid sequence described by SEQ ID NO: 53.

19. Claims 54 and 56-58 are rejected under 35 U.S.C. 102(b) as being anticipated by Takase et al. Claims 54 and 56-58 are drawn to the isolated, segregated δ subunit of the DNA polymerase III from *Escherichia coli.*

Takase et al. teach the *Escherichia coli rlpA* gene, which encodes a 36 kDa protein, its isolation and expression. Applicant's arguments, filed on January 5, 1998 as Paper No. 12, which reiterate the discussion of the prior art teachings of Takase et al. present in the Declaration under 37 CFR 1.132, filed on December 17, 1996 in the parent application, 08/279,058, have been fully considered but they are not persuasive. The claimed sequence, the 343 amino acids of SEQ ID NO: 9, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The claimed δ subunit, corresponding to SEQ ID NO: 9, is 100% identical to the translated nucleotide sequence taught by Takase et al. The Declaration under 37 CFR 1.132 filed on December 17, 1996 in the parent application, 08/279,058, is insufficient to overcome the rejection of claims 54 and 56-58 based upon Takase et al. as applied under 35 USC § 102(b) as set forth in the last Office action,

because the Declaration fails to set forth facts supporting the conclusions presented in the Declaration. Applicant asserts that the sequences disclosed by the instant application are not identical to the nucleotide and amino acid sequences taught by Takase et al. The Applicant cites references which support the assertion that the sequences taught by Takase et al. are erroneous. Regardless of the accuracy of the reported sequences, sequence analysis of the nucleotide sequences disclosed by Takase et al. show that a sequence taught by Takase et al. is 100% identical to the nucleotide sequence described by SEQ ID NO: 9, and corresponds to100% sequence identity with the amino acid sequence described by SEQ ID NO: 6. Furthermore, the references relied upon by the Applicant in the Declaration do not qualify as prior art. Thus, the teachings of these references are not available to demonstrate the state of the art at the time the invention was made. Therefore, the Declaration of December 17, 1996, with regard to the prior art teachings of Takase et al. does not present facts sufficient to overcome the rejection of claims 54 and 56-58 based upon Takase et al. as applied under 35 USC § 102(b).

20. Claims 59, 60, 64 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Takase et al. Claims 59, 60, 64 and 65 are drawn to the DNA molecules encoding the isolated, segregated δ subunit of the DNA polymerase III from *Escherichia coli*.

Takase et al. teach the *Escherichia coli rlpA* gene, which encodes a 36 kDa protein, its isolation and expression. Applicant's arguments, filed on January 5, 1998 as Paper No. 12, which reiterate the discussion of the prior art teachings of Takase et al. present in the Declaration under 37 CFR 1.132, filed on December 17, 1996 in the parent application, 08/279,058, have been fully

considered but they are not persuasive. The claimed sequence, the 1032 nucleotides of SEQ ID NO: 6, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The claimed DNA molecule, corresponding to SEQ ID NO: 6 and the nucleic acids encoding the protein described by SEQ ID NO: 9, is 100% identical to the nucleotide sequence taught by Takase et al. The Declaration under 37 CFR 1.132 filed on December 17, 1996 in the parent application, 08/279,058, is insufficient to overcome the rejection of claims 54 and 56-58 based upon Takase et al. as applied under 35 USC § 102(b) as set forth in the last Office action, because the Declaration fails to set forth facts supporting the conclusions presented in the Declaration. Applicant asserts that the sequences disclosed by the instant application are not identical to the nucleotide sequence taught by Takase et al. The Applicant cites references which support the assertion that the nucleotide sequence taught by Takase et al. is erroneous. Regardless of the accuracy of the reported sequences, sequence analysis of the nucleotide sequences disclosed by Takase et al. show that a sequence taught by Takase et al. is 100% identical to the nucleotide sequence described by SEQ ID NO: 9. Furthermore, the references relied upon by the Applicant in the Declaration do not qualify as prior art. Thus, the teachings of these references are not available to demonstrate the state of the art at the time the invention was made. Therefore, the Declaration of December 17, 1996, with regard to the prior art teachings of Takase et al. does not present facts sufficient to overcome the rejection of claims 59, 60, 64 and 65 based upon Takase et al. as applied under 35 USC § 102(b).

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. Claims 32-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshikawa et al. Claims 32-35 are drawn to the isolated, segregated ψ subunit of the DNA polymerase III from *Escherichia coli.*

Yoshikawa et al. teach the *E. coli rimI* gene. The claimed sequence, the 411 nucleotides of SEQ ID NO: 39, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The specific DNA molecule encoding the ψ subunit of DNA polymerase III disclosed in the instant application, which corresponds to SEQ ID NO: 39, is identical to the nucleotide sequence taught by Yoshikawa et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the nucleic acids taught by Yoshikawa et al. to produce the encoded proteins, ψ subunit of DNA polymerase III, because techniques for the expression of isolated genes were well known in the art at the time the invention was made, and the skilled artisan would have been motivated to isolate the expressed gene product.

23. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoshikawa et al. Claims 41 and 42 are drawn to expression systems for the ψ subunit of the DNA polymerase III from *Escherichia coli* and host cells transformed with nucleic acids encoding the isolated, segregated ψ subunit of the DNA polymerase III from *Escherichia coli.*

Yoshikawa et al. teach the *E. coli rimI* gene. The claimed sequence, the 411 nucleotides of SEQ ID NO: 39, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The specific DNA molecule encoding the ψ subunit of DNA polymerase III disclosed in the instant application, which corresponds to SEQ ID NO: 39, is identical to the nucleotide sequence taught by Yoshikawa et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the nucleic acids taught by Yoshikawa et al., because recombinant techniques for the expression of isolated genes were well known in the art at the time the invention was made.

24. Claims 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stirling et al. Claims 43-46 are drawn to the isolated, segregated χ subunit of the DNA polymerase III from *Escherichia coli.*

Stirling et al. teach the *Escherichia coli xerB* gene. The claimed protein sequence, the 147 amino acids described by SEQ ID NO: 53, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The χ subunit of DNA polymerase III disclosed in the instant

application, which corresponds to SEQ ID NO: 53, is identical to the translated nucleotide sequence taught by Stirling et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the nucleic acids taught by Stirling et al., because techniques for the expression of isolated genes were well known in the art at the time the invention was made, and the skilled artisan would have been motivated to isolate the expressed gene product.

25. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stirling et al. Claims 52 and 53 are drawn to the expression of the χ subunit of the DNA polymerase III from *Escherichia coli* and host cells transformed with nucleic acids encoding the χ subunit of the DNA polymerase III.

Stirling et al. teach the *Escherichia coli xerB* gene. The claimed nucleotide sequence, the 147 amino acids described by SEQ ID NO: 53, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The χ subunit of DNA polymerase III disclosed in the instant application, which corresponds to SEQ ID NO: 53, is identical to the translated nucleotide sequence taught by Stirling et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the nucleic acids taught by Stirling et al., because techniques for the expression of isolated genes were well known in the art at the time the invention was made, and the skilled artisan would have been motivated to isolate the expressed gene product.

26. Claims 54-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takase et al. Claims 54-58 are drawn to the isolated, segregated δ subunit of the DNA polymerase III from

Escherichia coli. Claims 64 and 65 are drawn to the expression of the δ subunit of the DNA polymerase III from *Escherichia coli* and host cells transformed with nucleic acids encoding the δ subunit of the DNA polymerase III.

Takase et al. teach the *Escherichia coli rlpA* gene, which encodes a 36 kDa protein, its isolation and expression. The claimed nucleotide sequence, the 1032 nucleotides described by SEQ ID NO: 6, were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. The DNA molecules encoding the δ subunit of DNA polymerase III disclosed in the instant application, which corresponds to SEQ ID NO: 6 , is identical to the nucleotide sequence taught by Takase et al. It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the nucleic acids taught by Takase et al., because techniques for the expression of isolated genes were well known in the art at the time the invention was made, and the skilled artisan would have been motivated to isolate the expressed gene product.

Double Patenting

27. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151

U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

28. Claims 5 and 7 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 32 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

29. Claim 8 rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 34 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

30. Claim 10 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 35 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

31. Claim 13 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 63 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

32. Claim 12 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 68 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

33. Claim 17 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 18 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

34. Claim 21 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 3 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

35. Claim 22 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 4 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

36. Claim 25 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 19 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

37. Claim 26 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 23 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

38. Claim 28 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 19 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

39. Claim 32 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 10 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

40. Claim 36 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 11 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

41. Claim 37 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 24 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

42. Claim 39 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 15 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

43. Claim 41 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 16 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

44. Claim 43 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 5 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

44. Claim 47 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 25 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

45. Claim 48 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 28 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

46. Claim 50 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 28 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

47. Claim 53 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 58 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

48. Claim 55 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 17 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

49. Claim 60 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 31 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

50. Claim 62 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 30 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

51. Claim 65 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 50 of prior U.S. Patent No. 08/279,058. This is a double patenting rejection.

52. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759

F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

53. Claim 9 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 34 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

54. Claim 13 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 64 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

55. Claim 17 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 71 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

56. Claim 21 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 75 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

57. Claim 23 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

58. Claim 32 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 73 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

59. Claim 38 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

60. Claim 41 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 40 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

61. Claim 43 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

62. Claim 47 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 25 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

63. Claim 49 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 47 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

64. Claim 53 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 60 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

65. Claim 65 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 4 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

66. Claim 63is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 61 of U.S. Patent No. 5,668,004. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Conclusion

67. No claims are allowed. Claims 8, 10, 17, 22, 26, 28, 48, and 62 are allowable over the prior art or record. A diligent search of electronic patent and scientific literature data bases revealed no prior art which either teaches or suggests the claimed proteins and DNA molecules limited by specific

SEQ ID Nos. In addition, the claimed sequences were compared with sequences of the prior art using MPSearch sequence analysis software employing the Smith-Waterman algorithm and using the default Table and a gap penalty of 6. No sequences which are taught by the prior art are identical to the claimed proteins and nucleic acid molecules. Thus, claims 8, 10, 17, 22, 26, 28, 48, and 62, which are limited to proteins and nucleic acids described by specific SEQ ID Nos, are free of the prior art.

68. The Group and Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1652.

69. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Einar Stole, Ph.D., whose telephone number is (703) -305-4507. The examiner can normally be reached Tuesday through Friday 6:30 a.m. to 5:00 p.m.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached on (703)-308-4216. The fax phone number for Technology Center 1600 is (703)-305-7401.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703)-308-0196.

Einar Stole, Ph.D.

Robert A. Wax
Supervisory Patent Examiner
Technology Center 1600

December 3, 1998